Synthesis of Non-Symmetrical Sulfamides

Using Burgess-Type Reagents

Specification

Cross Reference to Related Applications:

This is a non-provisional application claiming priority under 35 U.S.C. 119(e) from

5   copending US provisional application Serial No. 60/417,936, filed October 12, 2002.

Statement of Government Support:

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Field of Invention:

The invention is related to the synthesis of N,N'-differentiated sulfamides. More particularly, the invention is related to the synthesis of N,N'-differentiated sulfamides using amino alcohols and simple amines using Burgess-type reagents.

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Background:

Within the realm of proven pharmacophores, the sulfamide functional group (thiadiazine-1,1-dioxide) stands out as one of the most important structural motifs found in high affinity protein ligands and pharmaceutically useful agents. Indeed, a survey of

20   the recent patent literature reveals several hundred proprietary compounds having an impressive and diverse array of biological activities wherein a sulfamide group is incorporated within a suitable scaffold, often cyclic. For examples of such compounds, see R. J. Cherney, et al., **2002**, WO-2002028846; N.-Y. Shih, et al., **2001**, WO-2001044200;   G. M. Benson, et al., **2000**, WO-2000076501; R. D. Tung, et al.,

25   **1999**, US-5945413; I. Mcdonald, et al., **1999**, WO-9905141. Among the numerous applications of sulfamides, these agents have proven to be particularly effective as

inhibitors of key enzymes including HIV protease (W. Schaal, et al., *J. Med. Chem.* **2001**, *44*, 155 – 169; Spaltenstein, A.; et al. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159 – 1162; Bäckbro, K.; et al. *J. Med. Chem.* **1997**, *40*, 898 – 902; Hultén, J.; et al. *J. Med. Chem.* **1997**, *40*, 885 – 897) and serine protease (Kuang, R.; et al. *Bioorg. Med. Chem.*

5   **2000**, *8*, 1005 – 1016; Kuang, R.; et al. *J. Am. Chem. Soc.* **1999**, *121*, 8128 – 8129; Groutas, W.C.; et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2199 – 2204; Groutas, W. C.; et al. *Bioorg. Med. Chem.* **1998**, *6*, 661 – 671), and have demonstrated utility as both agonists and antagonists of critical molecular receptors such as those used to regulate endogenous levels of seratonin (Castro, J. L.; et al. *J. Med. Chem.* **1994**, *37*, 3023 –

10   3032) and histamine (Tozer, M. J.; et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3103 – 3108). Beyond their obvious significance in the treatment of disease, cyclic sulfamides have also been employed with considerable success as chiral ligands and auxiliaries (Pansare, S. V.; et al. *Synlett* **1998**, 623 – 624; Ahn, K. H.; et al. *Tetrahedron Lett.* **1992**, *33*, 6661 – 6664; Sartor, D.; et al. *Tetrahedron: Asymmetry* **1991**, *2*, 639 – 642;

15   Oppolzer, W.; et al. *Tetrahedron Lett.* **1991**, *32*, 4893 – 4896; Oppolzer, W.; et al. *Tetrahedron Lett.* **1991**, *32*, 61 – 64), and constitute an increasingly popular set of building blocks within the field of supramolecular chemistry (Hof, F.; et al. *Org. Lett.* **2001**, *3*, 4247 – 4249; Hof, F.; et al. *J. Am. Chem. Soc.* **2000**, *122*, 10991 – 10996; Gong, B.; et al. *J. Am. Chem. Soc.* **1999**, *121*, 9766 – 9767 and references cited in

20   each).

Despite the indisputable utility of these compounds, however, existing routes for their synthesis, particularly in a cyclic setting, are far from ideal. For example, typical procedures to fashion cyclosulfamides rely upon the reaction of a diamine with either

25   SO_2Cl_2 or $H_2NSO_2NH_2$ at elevated temperatures (Preiss, M. *Chem. Ber.* **1978**, *111*, 1915 – 1921; Rosenberg, S. H.; et al. *J. Med. Chem.* **1990**, *33*, 1582 – 1590; Dewynter, G.; et al. *Tetrahedron Lett.* **1991**, *32*, 6545 – 6548), conditions which often lead to a low yield of product due to the concomitant formation of polycondensation side-products. Equally problematic is the relative scarcity of suitable diamines for these

reactions from commercial sources and the difficulties associated with their laboratory preparation. An online search of the available chemicals directory revealed just slightly more than 200 unsubstituted 1,2-diamine substrates. By contrast, there are over 3000 unsubstituted β-amino alcohols. While these issues have led to the development of

5   several alternative protocols for sulfamide synthesis (Tozer, M. J.; et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3103 – 3108; Dougherty, J. M.; et al. *Tetrahedron* **2000**, *56*, 9781 – 9790; Dewynter, G.; et al. *Tetrahedron Lett.* **1997**, *38*, 8691 – 8694.), these additional synthetic technologies have proven amenable only to specific substrate classes and have not yet alleviated the need for multi-step protocols. Most significantly,

10   none of these methods has enabled the efficient and selective synthesis of non-symmetrical *N,N'*-disubstituted cyclosulfamides (**IV**, Figure 1), perhaps the most versatile class of these compounds for generating pharmaceutically-relevant molecular diversity.

15   What is needed is a general and widely applicable solution for the synthesis of these diverse classes of sulfamides for enabling the reliable and efficient formation of this highly desirable structural moiety (**IV**).

Summary:

20   A practical and high-yielding method for the efficient, one-step synthesis of diverse classes of *N,N'*-differentiated sulfamides employs a wide range of amino alcohols and simple amines using Burgess-type reagents. This synthetic technology constitutes a marked improvement over those currently in the literature, and extends the potential applications of sulfamides not only within chemical biology and medicinal

25   chemistry, but also in the fields of asymmetric synthesis and supramolecular chemistry. At a more fundamental level, this methodology serves to delineate new pathways in which the power of the Burgess reagent and its relatives can be applied to effect transformations of critical importance in chemical synthesis.

One aspect of the invention is directed to a process for the synthesizing a mono-protected, non-symmetrical cyclic sulfamide III from an amino alcohol I and Burgess reagent II represented by the following structures:
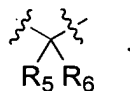
5

     I   II   III
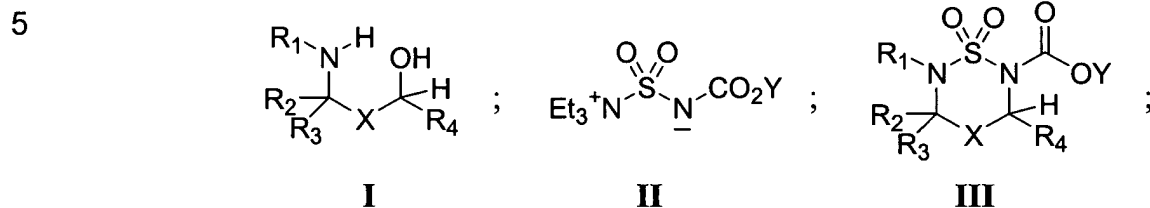
10   In the first step of the process, a solution of the amino alcohol I in a non-reactive solvent is contacted with a quantity of the Burgess reagent II under reaction conditions for producing sulfamide III. Then, after consuming amino alcohol I, the reaction is neutralized by dilution with a non-reactive solvent and treatment with an aqueous solution. Then, sulfamide III is isolated. In the above structures, X is absent or is a

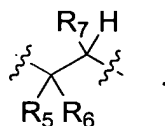15   diradical selected from the group consisting of the following structures:
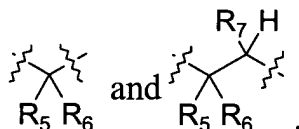
20   R_1 is a radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl, or is a diradical forming a ring with R_2; R_2 is a radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl, or is a diradical forming a ring with R_1 or R_3 or R_4, or is a diradical forming a part of an aromatic ring with R_5; R_3 is a radical selected from the group consisting of

25   hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl, or is a diradical forming a ring with R_1 or R_2 or R_5 or is a diradical forming half of a π-bond with R_6; R_4 is a radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, and benzyl or is a diradical forming a ring with R_2 or with R_5; R_5 is a radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl, or is a
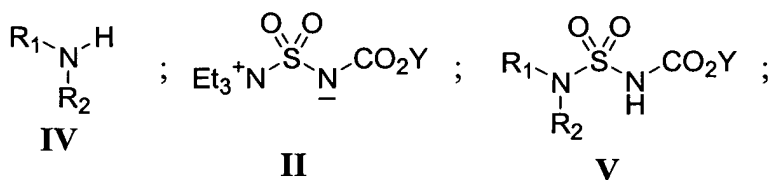
diradical forming a ring with R_1 or R_2 or R_6 or is a diradical forming part of an aromatic ring with R_3; R_6 is a radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl, or is a diradical forming a ring with R_1 or R_2 or R_5 or is a diradical forming half of a π-bond as part of an aromatic ring with R_3; R_7 is a

5   radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl; Y is a radical selected from the group consisting of -CH_3, -CH_2Ph and -$CH_2CH=CH_2$. The following provisos apply: If R_2 and R_5 are part of an aromatic ring; then R_3 and R_6 make up a full π-bond; and if X is absent, then R_3 cannot be half of a π-bond and R_2 is not part of an aromatic ring. In a preferred mode, the quantity of

10   Burgess reagent II is 2.5 equivalents. In an alternative preferred mode, X is absent. In another alternative preferred mode, X is a diradical with the following structure:

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In another alternative preferred mode, X is a diradical with the following structure:

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      Another aspect of the invention is directed to a process for synthesizing a mono-protected, non-symmetrical sulfamide V from an amine IV and Burgess reagent II represented by the following structures:

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In the first step of the process, a solution of the amine **IV** is contacted with a quantity of Burgess reagent **II** for under reaction conditions for producing sulfamide **V**. Then, the reaction his neutralized by dilution with a non-reactive solvent and treatment with an aqueous solution. Then, the sulfamide **V** is isolalted. In the above structures, R_1 is a

5   radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl, or a diradical forming a ring with R_2; R_2 is a radical selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, heteroaryl, alkylaryl, and benzyl, or a diradical forming a ring with R_1; and Y is a radical selected from the group consisting of -CH_3, -CH_2Ph and -$CH_2CH=CH_2$. In a preferred mode, the quantity of Burgess reagent

10   **II** is 1.25 equivalents.

Brief Description of Figures:

Figure 1 illustrates a conversion of amino alcohols (I) to cyclic sulfamides (III)
15   using Burgess (**1**) and related reagents (**2** and **3**) and further elaboration leading to non-symmetrically substituted, structurally diverse products (IV).

Figure 2 illustrates a chart showing the synthesis of a variety of non-symmetrical five-membered ring cyclic sulfamides from b-amino alcohols using the Burgess reagent
20   **1**.

Figure 3 illustrates a table showing the synthesis of non-symmetrical cyclic sulfamides from precursor amino alcohols using Burgess reagent (1).

Figure 4 illustrates a table showing the synthesis of mono-protected cyclic
25   sulfamides from precursor primary amino alcohols using Burgess reagent (1).

Figure 5 illustrates that Burgess reagent (1) can smoothly effect the generation of non-symmetrical, linear sulfamides from all classes of amines in excellent yield (Figure 5).

Figure 6 illustrates a table showing the deprotection of cyclic sulfamides to yield non-symmetrical, mono-substituted sulfamides.

Figure 7 is a table showing the synthesis of cyclic sulfamides by refluxing the
5   starting material and reagent in THF for two hours.

Detailed Description:

K. C. Nicolaou, et al. disclosed that β-amino alcohols can be smoothly synthesized with excellent chiral integrity from precursor diols through a novel
10   cyclization reaction initiated by Burgess reagent (**1**, Figure 1) (Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744 – 4745; Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 6135 – 6141; Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26 – 31) and related compounds (**2** and **3**) (Nicolaou, K. C.; et al. *Angew. Chem.* **2002**, *114*, 862 – 866; *Angew. Chem. Int. Ed.* **2002**, *41*, 834 – 838).   It
15   is disclosed herein that, upon application of this protocol to an amino alcohol starting material (I), a mono-protected, non-symmetrical cyclic sulfamide (III) results in a single, stereocontrolled operation through the delineated mechanism (Figure 1).   It is disclosed herein that this reaction course can be successfully realized in preference to the more typical rearrangement/dehydration pathways promoted by these reagents and
20   that subsequent deprotection of the carbamate in **III**, followed by substitution with an appropriate electrophile, then provides access to an assorted collection of sulfamides (**IV**) with the potential to incorporate diversity at all possible sites.   For references that disclose more typical rearrangement/dehydration pathways, see P. Taibe, S. Mobashery in *Encyclopedia of Reagents for Organic Synthesis, Vol. 5* (Ed.: L. A.
25   Paquette), John Wiley & Sons: Chichester, **1995**, pp. 3345 – 3347; and S. Burckhardt, *Synlett* **2000**, 559. Also, for some additional primary literature, see: Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224 – 5226; Wood, M. R.; Kim, J. Y.; Books, K. M. *Tetrahedron Lett.* **2002**, *43*, 3887 – 3890.)

To demonstrate this teaching, the methodology was employed using a representative set of commercially available secondary β-amino alcohols. Exposure of all substrates listed in Figure 2 to excess Burgess reagent (1) in refluxing THF for 8 hours led to the formation of the desired cyclic sulfamide product in high yield,

5 regardless of the nature of the group attached onto the amine. Of particular note, neither placing the amine in a hindered cyclic setting (entry 4) nor adding a bulky *t*-butyl substituent (entry 3) retarded product formation; this latter substrate constitutes a particularly effective test for the power of this synthetic technology, as starting materials bearing this functionality have, in general, proven recalcitrant to sulfamide formation

10 with currently available methods (Castro, J. L.; et al. *J. Med. Chem.* **1994**, *37*, 3023 – 3032). Of equal importance, all aniline-derived systems (entries 5 – 8) proved readily amenable to the cyclization process regardless of the electron-withdrawing (entries 6 and 7) or donating (entry 8) properties of the appended aromatic ring. These results are particularly indicative of the broad versatility of this intramolecular

15 Burgess-mediated cyclization, i.e., they demonstrate that the methodology may be employed in circumstances wherein the two nitrogen atoms of the sulfamide product are effectively differentiated. (Note: Amino alcohol substrates **14**, **16**, and **18** were prepared by the method of Heine, H. W.; et al. *J. Am. Chem. Soc.* **1954**, *76*, 2503. For alternative approaches to fashion these compounds, see: Rudesill, J. T.; et al. *J. Org.*

20 *Chem.* **1971**, *36*, 3071 – 3076.)

The limits of the Burgess-mediated sulfamide synthesis are more fully disclosed by the use of more challenging substrates. As shown in Figure 3, employing a chiral secondary alcohol (entry 1), even in a relatively hindered context, failed to engender

25 any particular difficulties (although extension of the reaction time beyond the standard 8 hours of heating was required to optimize yields), leading to **21** with clean inversion of configuration. A double cyclization seeking to generate a bis-sulfamide (**23**, entry 2) was also smoothly effected, with reduced yield in this case solely due to difficulties encountered during isolation of this polar product. Finally, following optimization of the

reaction conditions, extension of the sulfamide cyclization to ring sizes beyond the five-membered products formed in the previous examples also proved to be possible. Initial efforts in this regard focused on **24** (entry 3), wherein commencing the reaction at 0 °C for 1 hour then warming to ambient temperature for 5 hours led to the desired

5   product (**25**) in 45 % yield. All other conditions examined provided no improvement on this yield, giving only greater amounts of decomposition and leading us to conclude that the activated primary benzylic alcohol was responsible. Fundamentally, however, the formation of other sulfamide-containing rings should not prove to be as problematic if a non-benzylic alcohol is employed instead. For this reason, phenethylalcohol **26** was

10   examined and it was shown that the seven-membered ring analog (**27**, entry 4) was readily generated in 90 % yield through a cyclization reaction that is less favorable both enthalpically and entropically than that to form a six-membered ring. The smooth generation of **27** is additionally significant because this bicyclic product is analogous to the benzodiazepine motif, a molecular scaffold that has been the subject of intensive

15   biological investigations and the source of several clinically-employed agents (The literature pertaining to this field is so vast that it even has its own journal entitled *Benzodiazepine*. For additional general references, see information contained within: *Comprehensive Medicinal Chemistry* (Eds.: C. Hansch, P. G. Sammes, J. B. Taylor), Pergamon: Oxford, **1990**). In view of the successful cyclization of the latter two primary

20   aryl amine substrates in Figure 3, further extensions of this methodology were desired.

It is further disclosed that both sides of the resultant sulfamide product can be substituted in turn, leading to greater structural diversity. However, it is not preferred to employed primary aliphatic amino alcohols to this end. All four substrates examined

25   within this class (entries 1 – 4, Figure 4) gave rather disappointing yields of sulfamide products, leading either to decomposition or to the formation of side-products resulting from undesired rearrangements. In retrospect, however, the poor performance of these substrates in an intramolecular cyclization relative to their secondary amine counterparts is not so surprising, as in the absence of an additional alkyl or aryl

substituent, the nitrogen atom is less nucleophilic, requiring a longer reaction time and providing a greater opportunity for decomposition/rearrangement. The modest yields observed in these examples, however, do not really constitute a limitation in strategy, as the quantitative debenzylation of **7** (entry 2, Figure 2) using Pearlman's catalyst

5   provided a route to the same product **29** (entry 1, Figure 4), thus alleviating the need to start with ethanolamine (**28**). As such, this approach provides a tactic to sequentially substitute both sides of any cyclic sulfamide product, if so desired. Finally, in contrast with the results in the rest of Figure 4, when primary aliphatic amines were utilized in conjunction with a secondary benzylic alcohol (entries 5 and 6, Figure 4), product yields

10   were good when the reaction was performed at low temperature. As such, these unanticipated results suggest that there is a subtle interplay between substrate structure and particular reaction conditions to facilitate sulfamide formation in synthetically useful yield.

15   Beyond the synthesis of cyclic sulfamides, it is also disclosed herein that Burgess reagent (**1**) can smoothly effect the generation of non-symmetrical, linear sulfamides from all classes of amines in excellent yield (Figure 5). While this same conversion is more typically achieved by adding the amine to an appropriate chlorosulfonylisocyanate derivative, the present conditions provide a mild alternative

20   which avoids the use of these rather toxic and corrosive agents directly on the reaction substrate. For examples of the use of chlorosulfonylisocyanate derivatives, see Tozer, M. J.; et al., viz. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3103 – 3108; For an alternative synthesis of linear sulfamides, see, Davis, F. A.; et al.; *Tetrahedron Lett.* **1986**, *27*, 3957 – 3960.

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       All of the preceding examples of sulfamide synthesis in Figures 2 – 5 led to products with methyl carbamate protection. Accordingly, the Cbz and Alloc Burgess-type reagents (**2** and **3**, Figure 1) reported by Nicolaou et al. (Nicolaou, K. C.; et al. *Angew. Chem.* **2002**, *114*, 862 – 866; *Angew. Chem. Int. Ed.* **2002**, *41*, 834 –

838) were characterized with respect to their ability to perform the same transformations. All of the Burgess-type reagents reported by Nicolaou et al., including **2** and **3**, were readily isolable, and were purified through trituration with toluene and then stored at 0 °C for several months. (Note: The recent use of **3** in solution by a

5 Merck group, (Wood, M. R.; Kim, J. Y.; Books, K. M. *Tetrahedron Lett.* **2002**, *43*, 3887 – 3890), does not indicate that these reagents are unnstable in the solid form.) In all cases examined, these reagents provided the desired product in yields that were equivalent to those obtained with the original Burgess reagent (**1**). As such, this method of sulfamide synthesis, whether for cyclic or linear systems, can be tailored with

10 a variety of protecting groups to fit the particular needs of the test molecule. In line with several reports (Pete, B.; et al. *Heterocycles* **2000**, *53*, 665 – 673), it is also disclosed herein that subsequent deprotection (see Figure 6) is easily achieved with conventional procedures and readily followed by substitution of appropriate electrophiles (see Experimental Section). As such, the general and efficient synthesis of compounds

15 represented by structure **IV** (Figure 1) has been realized.

Experimental Section

Representative procedure:

20 The desired Burgess reagent (**1 – 3**, 1.25 mmol, 2.5 equiv) was added in one portion to a stirred solution of amino alcohol (0.5 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was then subjected to the conditions defined in the Figures. Upon completion, the reaction was diluted with CH_2Cl_2 (20 mL) and washed with 1N HCl (30 mL). The aqueous phase was re-extracted with CH_2Cl_2 (2 × 20 mL) and the combined

25 organic phase was dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography on silica gel then provided the desired products in the yields quoted.

Detailed Description of Figures:

Figure 1 shows the proposed conversion of amino alcohols (I) to cyclic sulfamides (III) using Burgess (1) and related reagents (2 and 3) and further elaboration leading to non-symmetrically substituted, structurally diverse products (IV). The sulfanamide nitrogen displaces the activated hydroxyl with inversion of configuration in

5   clean SN2 fashion. Further functionalization is possible for product III.

Figure 2 is a chart showing the synthesis of a variety of non-symmetrical five-membered ring cyclic sulfamides from b-amino alcohols using the Burgess reagent 1. A representative set of commercially available secondary β-amino alcohols was

10   investigated. Exposure of all substrates listed in Figure 2 to excess Burgess reagent (1) in refluxing THF for 8 hours led to the formation of the desired cyclic sulfamide product in high yield, regardless of the nature of the group attached onto the amine. Of particular note, neither placing the amine in a hindered cyclic setting (entry 4) nor adding a bulky t-butyl substituent (entry 3) retarded product formation. All

15   aniline-derived systems (entries 5 – 8) proved readily amenable to the cyclization process regardless of the electron- withdrawing (entries 6 and 7) or donating (entry 8) properties of the appended aromatic ring, results indicative of the versatility of this intramolecular Burgess-mediated cyclization.

20   Figure 3 is a table showing the synthesis of non-symmetrical cyclic sulfamides from precursor amino alcohols using Burgess reagent (1). Here there was exploration of additional substrate classes and development of optimized reaction conditions. Employing a chiral secondary alcohol (entry 1, 20) failed to produce any particular difficulties (although extension of the reaction time beyond the standard 8 hours of

25   heating was required to optimize yields), leading to 21 with clean inversion of configuration.

Figure 4 is a table showing the synthesis of mono-protected cyclic sulfamides from precursor primary amino alcohols using Burgess reagent (1). All four substrates

examined within this class (entries 1 – 4) gave rather disappointing yields of sulfamide products, leading either to decomposition or to the formation of side-products resulting from undesired rearrangements. The poor performance of these substrates in an intramolecular cyclization relative to their secondary amine counterparts is not so

5   surprising, as in the absence of an additional alkyl or aryl substituent, the nitrogen atom is less nucleophilic, requiring a longer reaction time and providing a greater opportunity for decomposition/rearrangement.

Figure 5 shows that Burgess reagent (1) can smoothly effect the generation of

10   non-symmetrical, linear sulfamides from all classes of amines in excellent yield (Figure 5). While this same conversion is more typically achieved by adding the amine to an appropriate chlorosulfonylisocyanate derivative (Tozer, M. J.; et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3103 – 3108; these conditions provide a mild alternative which avoids the use of these rather toxic and corrosive agents directly on the reaction substrate. In this

15   case, only 1.3 equivalents of Burgess reagent is used to facilitate the reaction process.

Figure 6 is a table showing the deprotection of cyclic sulfamides to yield non-symmetrical, mono-substituted sulfamides. (a) Yield in parentheses is that for synthesis of the starting material; (b) NaOH, MeOH:H_2O (2:1), 25 °C, 2 hours; (c)

20   Pd(OAc)$_2$ (10 mol %), 3,3',3''-phosphinidynetris(benzenesulfonic acid) trisodium salt (20 mol %), HNEt$_2$ (40 equiv), MeCN:H_2O (1:1), 25 °C, 15 min; (d) 10% Pd/C, H_2 (60 psi), EtOH:EtOAc (4:1), 25 °C, 2 hours.

Figure 7 is a table showing the synthesis of cyclic sulfamides by refluxing the

25   starting material and reagent in THF for two hours. The preparation of the substrates is shown at the bottom of the page. Imine formation with the appropriate aromatic aldehyde is followed by reduction with cyanoborohydride to give the desired aminol starting material. All 3 types of rings tested gave good results.